REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As indicated in the Office Action Summary, claims 1-39 are pending. Claims 2 and 9 are canceled by way of this Amendment. Applicants reserve the right to file a continuation or divisional application directed to any subject matter deleted by way of this Amendment. Claims 1, 4-12, 17-18, 20, 30 and 39 are amended herein, to clarify the claimed subject matter and attend to formalities of spelling and grammar. Basis for these amendments may be found throughout the specification and claims as-filed, especially in claim 9, pages 13-14 and page 18. Thus, no new matter is presented by way of this Amendment.

Claim Objections

Claim 5 is objected to because it is purportedly grammatically incorrect. Claim 5 has been amended herein, as suggested by the Examiner, to replace "modifying" with the "modified".

Claim 6 is objected to because "Cricks" is purportedly misspelled. Claim 6 has been amended herein to recite proper spelling. Claim 7 is objected to because the phrases "a chimeric oligonucleotide DNA/2'OMeRNA type" and "at least single mismatched oligonucleotide" are purportedly grammatically incorrect. Claim 7 has been amended

herein to address the issues of grammar. Claim 10 is objected to because the phrase "partially responsible of an eye inherited pathology" is grammatically incorrect. Claim 10 has been amended herein to address the issues of grammar.

Claim 12 is objected to because "intraviteal" is purportedly misspelled. Claim 12 has been amended herein to recite the proper spelling. Claim 20 is objected to because the phrase "electrically connection" in part (A) is purportedly grammatically incorrect. Claim 20 also purportedly lacks an article preceding the noun "bi-state switch" in part (H). Claim 20 also purportedly unnecessarily includes a comma between the words "flowing" and "between" in part (0). Claim 20 has been amended herein to address these issues of grammar.

Claim 30 is objected to because it purportedly contains non-elected subject matter, *i.e.*, any oligonucleotide capable of reverting a mutation in the human RP1 protein sequence, and an any oligonucleotide capable of reverting an R677-STOP mutation in human opsin. Claim 30 has been amended herein to remove reference to this subject matter.

Thus, Applicants submit that these objections are obviated.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-12, 17, 18, 20, 21, 30, and 39 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly containing subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in *Ex parte Forman* (230 USPQ 546 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As, the Office is aware, "[a] patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. § 112, first paragraph. Thus, not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be. *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (Bd. Pat. App. & Int. 1992). Applicants submit that the specification provides adequate description of how to use the presently claimed invention, as amended herein.

As amended by way of the present Amendment, the claims now recite methods of delivering a chimeric oligonucleotide in target cells of a non-human or animal eye tissue. Applicants note that the object of the present invention is to provide a new technique for delivering a chimeric oligonucleotide into a specific target, *i.e.*,the gene for eye repair. Also, Applicants note that techniques such as iontophoresis are already known in the art, as described, for example, in U.S. Patent No. 6,154,671, cited in the present specification.

The inventors have demonstrated that the iontophoresis is an efficient method to deliver chimeric oligonucleotide into a specific target, the eye for gene repair.

Turning now to the factors to consider in evaluating the need (or absence of need) for "undue experimentation", Applicants note the following.

Nature of the Invention and Breadth of the Claims

The Office Action states that claims 1-12, 20, and 21 are broadly drawn to methods of introducing a any chimeric oligonucleotide targeting any gene into an animal tissue *in vivo* and claims 9-12 limit the site of delivery, but not the identity of the target gene. Applicants submit that the amendments to the claims, made herein, provide clarification as to the target gene of interest.

State of the Art, Predictability of the Art, and Level of Skill of Those in the Art

The Office Action states that the relevant field is unpredictable. Applicants respectfully traverse.

Applicants submit that the articles cited in the outstanding Office Action as illustrating the state of the art of chimeraplasty at the time the invention was filed relate to chimeraplasty experiments that failed. Most of the experiments in the cited references were only prepared *in vitro*, (only one was performed *in vivo)*. None of the experiments set forth in the cited references had been conducted *in vivo* in the eye, a very specific living

tissue. In fact, most techniques developed to deliver a drug into the eye dramatically differ from the techniques used for other body tissues and organs.

Further, with regard to all the techniques used to deliver RNA/DNA oligonucleotide (RDO) *in vitro* and cited in the Office Action, none of them have tried iontophoresis to deliver RDO. Appliants draw the Examiner to a more recent article from Liang *et al., Eur. J. Biochem.* 269, 5753-5758 (2002) (enclosed herewith) regarding optimization of delivery systems of RDO. This reference describes the first designed RDOs for targeted gene correction in 1996. Since that time, it has been realized that optimizing the length and structure of the RDOs is crucial, and that another key step toward clinical application is to optimize RDO delivery vectors. Only with the development of carrier systems can RDOs be applied to functional genomics and used in human gene therapy.

By way of further explanation, Applicants submit reference which focus on ocular gene transfer or gene therapy using iontophoresis, and assess the progress made to further this method. *See* Berdugo M. *et al., Antisense Nucleic Acid Drug Dev.* 2003 Apr. 13(2):107-14 (abstract enclosed herewith) about ODN delivery in the eye, Kurz D. *et al., Ophthalmol. Clin. North Am.* 2002 Sep. 15(3):405-10 (abstract enclosed herewith) about different technique to transfer genes to the retina, Voigt M. *et al., Biochem. Biophys. Res. Commun.* 2002 Jul. 12; 295(2):336-41 (enclosed herewith) also about ODN delivery in the eye.

Guidance and Examples in the Specification

The Office Action states that the specification provides no new guidance with respect to the general structural characteristics of chimeraplasts.

Applicants submit that the most significant proof of concept is rod-photoreceptor survival. While gene reparation evidence may suffer from artifacts and that other techniques could be used, Applicants note that photoreceptor survival is a significant result, and the murine model was selected for this reason.

Amount of Experimentation Required to Practice the Invention

The Office Action argues that in view of the uncertain state of the art at the time of the invention, the high level of unpredictability associated with chimeraplasty, the persistent and routine failure of those of skill in the art to obtain positive results using chimeraplasty or to reproduce apparently positive results published in the art, one of skill in the art would have had to perform undue experimentation in order to use the invention as intended. Applicants traverse.

Specifically, the Office Actions states that there is no such thing as a K296E mutation of human RP1, and one of skill in the art could not make an oligonucleotide capable of reverting such a mutation. Applicants agree that K296E mutation occurs in rhodopsin (named also opsin) instead of in RP1 (*see* article from Sohcki M., Human mutation 17:42-51, 2001, as cited in the present specification). However, there is a mismatch in the specification, as noted by the Examiner. In fact, the mutation K296E

concerns the rhodopsin gene. Applicants submit that it is clear in view of the specification that the mutation K296E concerns the rhodopsin gene (see page 13, lines 10 "... the missence mutation of the active-site Lys 296 in that rhodopsin gene ...") and the enclosed abstracts Keen *et al., Genomics* 1991 and Robinson *et al., Neuron*, 1992.

With regard to claim 2, Applicants note that this claim has been deleted herein.

With regard to claim 5, Applicants note that gene repair is the main interest of chimeraplasty, and thus it would be inefficient to correct the products of a genetic defect (protein) instead of correcting the genetic defect itself. Claim 5 has been amended herein to recite the modification of the gene rather than the modification of the product of the gene, to clarify this point.

Claim 1 has been amended herein to provide clarification regarding the use a non-mutagenic chimeraplast oligonucleotide.

Claims 1-12, 17, 18, 20, and 21 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Office Action states that practice of the methods of claims 8, 11, and 12 requires knowledge of the genus of sequences of mutated genes that are responsible for any inherited pathology, and that practice of the method of claim 10 requires knowledge of the

genus of genes that, when mutated, are at least partially responsible for an eye inherited pathology. Applicants traverse.

The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the skilled artisan that the inventor had possession of the invention at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language. *See Ex parte Remark*, 15 U.S.P.Q.2d 1498, 1506 (Pat. Bd. App. & Int. 1990). Applicants submit that the specification provides adequate written description for the claimed invention, as amended herein, for at least the following reasons.

Applicants note that pathology may have multiple cause. However, the present invention intends not to list all the potential target for gene repair. Rather, the present invention intends to describe a step by step method that allow targeted gene repair in the eye and more specifically in the retina. To this end, Applicants have amended the claims, and submit that the claims as amended are fully supported by the specification.

Applicants request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-12, 17, 18, 20, 21, 30, and 39 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite.

Claim 1 and dependents are purportedly indefinite because they draw a distinction between humans and animals, depicting them as alternatives. The Examiner argues that humans are members of the kingdom of *Animalia*, and are by definition animals, so the claims are unclear. To this end, the claims are amended herein to recite "a non-human animal".

Claim 1 and dependents are purportedly indefinite for the recitation of the phrase "the patient tissue" without proper antecedent basis. A suggested by the Examiner, the claims have been amended herein to recite"animal" rather than "patient".

Claim 2 stand rejected for purportedly failing to further limit claim 1. Claim 2 is deleted by way of this Amendment.

Claim 4 is purportedly indefinite for the recitation of the term "specifically". Claim 4 is amended herein to remove this term.

Claims 7, 8, 11, 12, 30, and 39 are purportedly indefinite for the recitation of the phrase "chimeric oligonucleotide DNA/2'OMeRNA type", and/or the phrase chimeric oligonucleotide DNA/2'OMeRNA, and/or the phrase "DNA/2'OMeRNA". As suggested by the Examiner, the claims have been amended herein to recite a chimeric oligonucleotide comprising DNA and 2' methoxy RNA.

Claims 7, 8, 11, 12, 30, and 39 stand rejected because the required organization of the chimeric oligonucleotide is purportedly unclear.

Applicants submit that the organization of the chimeric oligonucleotide is defined in the in the references cited in the specification (for example in Yoon *et al., Proc. Natl. Acad. Sci. USA,* Vol. 93, pp. 2071-2076, March 1996. Thus, this organization is known the skilled artisan.

Specifically, as known to the skilled artisan and as mentioned in U.S. Patent No. 5,760,012 cited in the present specification (see pages 10-12, part D, and page 17, example 2, first paragraph, enclosed herewith), the chimeric oligonucleotides DNA/2'O-MeRNA used to gene repair is generally a 3', 5'-linked nucleic acid, having one 3' and one 5' terminus and generally having the 3' and 5' terminus covalently linked. The DNA/2'O-MeRNA contains unpaired nucleotides, which form two hair-pin turns, which divide the DNA/2'O-MeRNA into two strands. At least 15 bases of the first strand are Watson-Crick paired to bases of the second strand. The DNA/2'O-MeRNA is further characterized by the presence of a plurality of segments of at least three contiguous bases comprised of 2'-O or 2'-alkylether ribose nucleotides which are paired to deoxyribonucleotides of the second strand. The chimeric oligonucleotides DNA/2'O-MeRNA used in the present invention (SEQ ID NO: 3) are composed of DNA residues with two intervening blocks of ten 2'-0-methyl RNA residues flanking a short stretch of five DNA residues. When the molecule is folded into the duplex conformation, one strand contains only DNA residues while the other strand contains the RNA/DNA blocks. In the case of the chimeric oligonucleotide having the sequence SEQ ID NO: 3 of the present invention, the internal sequence is complementary to the target gene over a

stretch of 25 residues that span the site of the b-subunit of the cGMP-phosphodiesterase mutation, with the exception of a single base. The five DNA residues flanked by RNA residues were centered about the mutant residue.

Claim 8 stands rejected because it is purportedly unclear which DNA/RNA sequence is referred to by "that DNA/RNA sequence." Claim 8 also stands rejected because there is purportedly no clear antecedent basis for "that mutation which is desired to be reverted". Claim 8 has been amended herein to recite a "chimeric oligonucleotide containing DNA and 2'methoxy RNA and wherein said target gene is selected from the group consisting of cGMP phosphodiesterase, beta-subunit, RP1, opsin and HIF1α gene" to clarify the claimed subject matter.

Claim 10 stands rejected because it is purportedly unclear whether "epidermal and dermal tissue" is a single species of the Markush group, or if epidermal is intended to be separate species from dermal. Applicants note that claim 10 does not recite "epidermal and dermal tissue", but that claim 9 does recite this phrase. Claim 9 has been canceled by way of this Amendment.

Claims 20 and 21 are purportedly indefinite for the recitation of the term "the iontophoresis system used in step b)" without antecedent basis. Claim 20 is purportedly indefinite because for recitation of the phrase "the chemical species without antecedent basis" in part (B). Claim 20 is purportedly indefinite for the recitation of the term "said electrode", "said iontotherapuetic delivery", "the electrode", "said ionized pharmaceutical", and "said membrane" without proper antecedent basis in part (G). Claim

20 is purportedly indefinite for the recitation of the term "the effects" without antecedent basis in part (L). Claims 20 has been amended herein to address these issues of antecedent basis.

Applicants request that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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